

Recent Advances in Cardiopulmonary Resuscitation: Cardiocerebral Resuscitation

Gordon A. Ewy, and Karl B. Kern
J. Am. Coll. Cardiol. 2009;53;149-157
doi:10.1016/j.jacc.2008.05.066

This information is current as of March 10, 2010

The online version of this article, along with updated information and services, is located on the World Wide Web at:
<http://content.onlinejacc.org/cgi/content/full/53/2/149>

JACC

JOURNAL of the AMERICAN COLLEGE of CARDIOLOGY



STATE-OF-THE-ART PAPERS

Recent Advances in Cardiopulmonary Resuscitation

Cardiocerebral Resuscitation

Gordon A. Ewy, MD, FACC,* Karl B. Kern, MD, FACC†

Tucson, Arizona

Cardiocerebral resuscitation (CCR) is a new approach for resuscitation of patients with cardiac arrest. It is composed of 3 components: 1) continuous chest compressions for bystander resuscitation; 2) a new emergency medical services (EMS) algorithm; and 3) aggressive post-resuscitation care. The first 2 components of CCR were first instituted in 2003 in Tucson, Arizona; in 2004 in the Rock and Walworth counties of Wisconsin; and in 2005 in the Phoenix, Arizona, metropolitan area. The CCR method has been shown to dramatically improve survival in the subset of patients most likely to survive: those with witnessed arrest and shockable rhythm on arrival of EMS. The CCR method advocates continuous chest compressions without mouth-to-mouth ventilations for witnessed cardiac arrest. It advocates either prompt or delayed defibrillation, based on the 3-phase time-sensitive model of ventricular fibrillation (VF) articulated by Weisfeldt and Becker. For bystanders with access to automated external defibrillators and EMS personnel who arrive during the electrical phase (i.e., the first 4 or 5 min of VF arrest), the delivery of prompt defibrillator shock is recommended. However, EMS personnel most often arrive after the electrical phase—in the circulatory phase of VF arrest. During the circulatory phase of VF arrest, the fibrillating myocardium has used up much of its energy stores, and chest compressions that perfuse the heart are mandatory prior to and immediately after a defibrillator shock. Endotracheal intubation is delayed, excessive ventilations are avoided, and early-administration epinephrine is advocated. (J Am Coll Cardiol 2009; 53:149–57) © 2009 by the American College of Cardiology Foundation

Developed by the University of Arizona Sarver Heart Center Resuscitation Group, cardiocerebral resuscitation (CCR) (Table 1) is a new approach to the resuscitation of patients with cardiac arrest that significantly improves neurologically intact survival (1–5). Based on decades of resuscitation research in our experimental laboratory, and our interpretation and integration of the national and international scientific published reports on resuscitation, we concluded in 2003 that we could no longer follow the national guidelines because we were convinced that they were not optimal (6,7). CCR was instituted in Tucson, Arizona, in 2003; in the Rock and Walworth counties in Wisconsin in 2004; in selected metropolitan cities of Arizona in 2005; and in many fire departments throughout Arizona in 2006 to 2007 (2–4). In each area, survival of patients with witnessed out-of-hospital cardiac arrest (OHCA) and shockable rhythm dramatically improved (3–5).

The CCR method is composed of 3 important components: 1) continuous chest compressions (CCCs) for bystander resuscitation; 2) new emergency medical services (EMS) advanced cardiac life support (ACLS) algorithm;

and 3) aggressive post-resuscitation care including therapeutic hypothermia and early catheterization/intervention (Table 1).

CCR advocates CCC cardiopulmonary resuscitation (CPR) without mouth-to-mouth ventilations for witnessed cardiac arrest. For ACLS, either prompt or delayed defibrillation is advocated, based on the 3-phase time-sensitive model of ventricular fibrillation (VF) articulated by Weisfeldt and Becker (8). For bystanders with access to an automated external defibrillator (AED) and EMS personnel who arrive during the electrical phase (i.e., the first 4 or 5 min of VF arrest), prompt defibrillator shock is recommended (9). However, EMS personnel most often arrive after the electrical phase—in the circulatory phase of VF arrest (10). During the circulatory phase of VF arrest, the fibrillating myocardium has used up much of its energy stores, and chest compressions that perfuse the heart are necessary and therefore advocated prior to and immediately after a defibrillator shock (1,11,12). Endotracheal intubation is delayed, excessive ventilations are avoided, and early administration of epinephrine is advocated (Fig. 1) (1,3). To avoid excessive ventilations of patients with cardiac arrest, which are common by both physicians and paramedics, the initial approach to ventilation is passive oxygen insufflation (Fig. 1) (13,14). The CCR method has been shown to dramatically improve survival in the subset of patients most

From the *University of Arizona Sarver Heart Center and the †Cardiac Catheterization Laboratories, University of Arizona College of Medicine, Tucson, Arizona.

Manuscript received March 12, 2008; revised manuscript received May 22, 2008, accepted May 27, 2008.

Abbreviations and Acronyms

- ACLS** = advanced cardiac life support
- AED** = automatic external defibrillator
- CCC** = continuous chest compression
- CCR** = cardiocerebral resuscitation
- CPR** = cardiopulmonary resuscitation
- ECG** = electrocardiograph
- EMS** = emergency medical services
- OHCA** = out-of-hospital cardiac arrest
- PCI** = percutaneous coronary intervention
- PEA** = pulseless electrical activity
- STEMI** = ST-segment elevation myocardial infarction
- VF** = ventricular fibrillation

likely to survive—those with witnessed arrest and a shockable rhythm (3–5).

For comatose patients post-resuscitation, hypothermia and early cardiac catheterization (unless contraindicated), even in the absence of classic electrocardiograph (ECG) signs of infarction or ischemia, are recommended. Because these therapies are not available in all hospitals, the Arizona Bureau of Emergency Medical Services and Trauma is designating “Cardiac Arrest” hospitals, much as “Trauma One” hospitals are designated. This way, resuscitated but comatose patients post-resuscitation will have the best chance of neurologically normal recovery.

CCR is not recommended for individuals with respiratory arrest. These individuals require early ventilations; until alternatives to the current approach are

shown to be better, guidelines recommend CPR for individuals with respiratory arrest (15).

CPR: Survival Rates Disappointing

Sudden cardiac death is a leading cause of mortality in the industrialized nations of the world and, accordingly, is a major public health problem (16,17). In the U.S., as a cause of death, it is second only to all cancer deaths combined (18). In spite of the development of standards in 1974 (19), standards and guidelines in 1980 (20), guidelines in 1992 (21), and updates of the guidelines in 2000 (7) for emergency cardiac care that included CPR and ACLS, with rare exceptions, the survival rate of victims of OHCA remains disappointingly low. The reported overall survival rates in Chicago, Illinois, in 1987; in New York in 1990; and in Los Angeles, California, in 2000 were each just higher than 1%, a result that is near that described as medical futility (22). Survival rates after OHCA are better in those who receive bystander CPR (Table 2) (23–28) and in those with rapid response times (29). In a recent report by Rea et al. (29), survival to discharge in the subset of patients with witnessed OHCA and VF improved when they changed their EMS protocol to provide a single shock followed by immediate chest compressions (without a pulse check or reanalysis of post-shock rhythm) as opposed to the previously recommended stacked shocks. Survival increased by nearly 40% (29).

One contributor to poor survival is that CPR has heretofore been advocated for 2 distinctly different pathophysiologic conditions: primary cardiac arrest, in which the

arterial blood is almost always fully oxygenated at the time of the cardiac arrest, and cardiac arrest secondary to respiratory failure, in which the initially normal cardiac output in spite of the lack of ventilation leads to severe hypoxemia, hypotension, and secondary cardiac arrest (1). Therefore, different approaches are no doubt necessary.

Bystander-Initiated Resuscitation Efforts Are Critical

The initiations of bystander resuscitations, especially when begun within 1 min of the arrest, markedly improve survival (30). In 1 analysis, survival was more than 4 times greater in patients who received early bystander CPR (31). However, in this age of universal precautions, with few exceptions, only 1 in 4 or 5 patients with OHCA currently receive bystander-initiated CPR. This is a major health problem.

“Rescue Breathing” for Cardiac Arrest Is a Misnomer

“Rescue breathing” as previously and currently advocated is a misnomer (7,15,19–21,32) because this requirement dramatically decreases the survival chances of patients with witnessed cardiac arrest receiving bystander-initiated resuscitation, and bystander attempts at assisted ventilation have been shown to decrease the chance of survival in the subset of subjects with cardiac arrest who have the greatest chance of survival—namely those with witnessed cardiac arrest and shockable rhythm (33,34).

The requirement for mouth-to-mouth ventilations has several major drawbacks for patients with cardiac arrest. First, it decreases the number of individuals with cardiac arrest who receive prompt bystander resuscitation efforts. Most bystanders who witness a cardiac arrest are willing to alert EMS but are not willing to initiate bystander rescue efforts because they are not willing to perform mouth-to-mouth ventilation. Training and certification in basic life

Table 1 Three Pillars of Cardiocerebral Resuscitation

1. CCC (compression-only cardiopulmonary resuscitation) by anyone who witnesses unexpected collapse with abnormal breathing (cardiac arrest).
2. Cardiocerebral resuscitation by emergency medical services (arriving during circulatory phase of untreated ventricular fibrillation [e.g., >5 min])
 - a. 200 CCCs (delay intubation, second person applies defibrillation pads and initiates passive oxygen insufflation).
 - b. Single direct current shock if indicated without post-defibrillation pulse check.
 - c. 200 CCCs prior to pulse check or rhythm analysis.
 - d. Epinephrine (intravenous or intraosseous) as soon as possible.
 - e. Repeat (b) and (c) 3 times. Intubate if no return of spontaneous circulation after 3 cycles.
 - f. Continue resuscitation efforts with minimal interruptions of chest compressions until successful or pronounced dead.
3. Post-resuscitation care to include mild hypothermia (32 °C to 34 °C) for patients in coma post-arrest. Urgent cardiac catheterization and percutaneous coronary intervention unless contraindicated.

CCC = continuous chest compression.

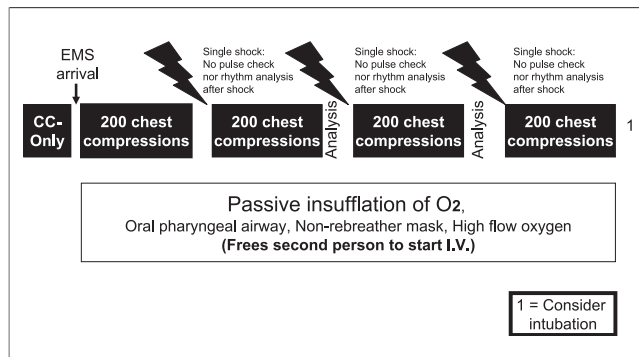


Figure 1 Cardiocerebral Resuscitation: EMS Protocol for Out-of-Hospital Cardiac Arrest

Cardiocerebral resuscitation protocol for emergency medical services (EMS) providers once they arrive on the scene. Continuous chest compressions (CCCs) only indicates that a bystander is doing adequate CCCs. If so, the paramedics do not perform the initial 200 CCCs before the first electrocardiograph rhythm analysis with their automated external defibrillator or defibrillator that has the ability to record the electrocardiographic rhythm via the electrode paddles or pads. If there is no bystander doing CCCs or if there is and CCCs are deemed to be inadequate by the EMS personnel, 200 forceful CCCs are carried out with full chest wall release after each compression. The compressions are given at a rate of 100 compressions/min before electrocardiographic analysis. When appropriate, a defibrillator shock (indicated by the lightning symbol) is given. Following the defibrillator shock, the EMS personnel should not check for pulse or electrocardiographic rhythm but rather immediately initiate another 200 CCCs. After these 400 CCCs, they perform an analysis of the electrocardiographic rhythm and ascertain the presence or absence of a pulse. Three such sequences are completed prior to intubation. Intubation as well as bag-valve-mask ventilations are initially prohibited. This is because intubation delays the initiation of CCCs, and both result in excessive ventilations. Rather, the patient is treated with passive insufflation of oxygen by placing an oral pharyngeal airway and a nonrebreather mask and attaching high-flow (10 to 15 l/min) oxygen. Intubation is recommended if the patient does not have a shockable rhythm or after 3 single shocks, each followed by 200 CCCs, and a perfusing rhythm is still not present. If the patient is unconscious or not breathing adequately, intubation is recommended prior to transfer. 1 = consider intubation.

support does not change this fact. Unfortunately, as late as January 2008, a scientific statement from the American Heart Association (AHA) that recognized the crucial need to increase bystander resuscitation had little new to offer but more vigorous layperson training (35). Bystanders have long been willing to do chest compression-only or CCC CPR for such individuals, an approach that has been shown to be dramatically better than doing nothing (36).

The second reason requiring mouth-to-mouth ventilations is not optimal is that even the best attempts by laypersons to do “rescue breathing” result in inordinately long interruptions of chest compressions during cardiac arrest (37), and long interruptions of chest compressions decrease neurologically normal survival (38). For single laypeople recently certified in basic CPR, chest compressions are interrupted an average of 16 s to perform the recommended “2 quick breaths” (37). Recognizing the importance of delivering more chest compressions with less interruptions, the 2005 CPR guidelines were changed, recommending an increased compression to perfusion ratio (30:2), based not on experimental survival data but on consensus (15). Normal neurologic survival in our laboratory model of clinically realistic OHCA was better with CCC than with 30:2 compressions to ventilations when each set of chest compressions were interrupted for a realistic 16 s to deliver the 2 recommended assisted ventilations (39). During chest compressions for cardiac arrest, the forward blood flow is so marginal that any interruption of chest compressions decreases vital blood flow to the brain.

A third reason that requiring mouth-to-mouth ventilations by bystanders is not optimal is that even if chest compressions are not interrupted, positive-pressure ventilation during cardiac arrest increases intrathoracic pressure, thereby decreasing venous return to the thorax and subsequent perfusion of the heart and the brain (40). This phenomenon is made worse when forceful ventilations are given while the chest is being compressed (14).

Another concern with attempted rescue breathing during bystander CPR is the amount of air that enters the stomach rather than the lungs (41). Mouth-to-mouth ventilation can cause regurgitation in nearly 50% of patients, probably because of gastric insufflation (42). Lawes and Baskett (43) reported that 46% of nonsurvivors from cardiac arrest had full stomachs and 29% had evidence of pulmonary aspiration. In another study, 39% of patients receiving mouth-to-mouth ventilations had signs of gastric regurgitation at the time of intubation (44). The evidence that immediate ventilations are necessary for sudden cardiac arrest victims is based neither on data during cardiac arrest nor on logic,

Table 2 Clinical Bystander CPR Observations

Location (Year) (Ref. #)	No CPR	CC Only	CC + RB
Survival after out-of-hospital cardiac arrest according to bystander response			
Belgium (1993) (23)	123/2,055 (6%)	17/116 (15%)	71/443 (16%)
Seattle (2000) (24)		32/240 (15%)	29/278 (10%)
the Netherlands (2001) (25)	26/429 (6%)	6/41 (15%)	61/437 (14%)
SOS-KANTO (2007) (26)	63/2,917 (2%)	27/439 (6%)	30/712 (4%)
Utstein Osaka (2007) (27)	70/2,817 (3%)	19/441 (4%)	25/617 (4%)
Sweden (2007) (28)		591/8,209 (7%)	77/1,145 (7%)
Survival after witnessed out-of-hospital cardiac arrest and shockable			
SOS-KANTO (2007) (26)	45/549 (8%)	24/124 (19%)	23/205 (11%)*
Utstein Osaka (2007) (27)	44/535 (8%)	14/122 (12%)	18/161 (11%)*

CC = chest compression; CPR = cardiopulmonary resuscitation; RB = rescue breathing.

because with the onset of VF-induced arrest, the pulmonary veins, left heart, and entire arterial system are filled with oxygenated blood. The important issue is to circulate such oxygenated blood to the tissues, particularly the brain and myocardium. The recommended ventilations do not increase arterial saturation—they only further delay the onset of critical chest compressions (45).

Finally, mouth-to-mouth ventilations are not necessary in a significant number of victims of witnessed cardiac arrest because they initially gasp, and if chest compressions are started early and continued, many victims will continue to gasp and thereby provide physiologic ventilation (i.e., ventilations with decreasing intrathoracic pressures that facilitate venous return to the chest and heart). If chest compressions are initiated early, many subjects who are not gasping will begin to gasp. Because of these facts, it is important that bystanders be taught that “abnormal breathing” is either no or abnormal respirations and that abnormal respirations are apnea or gasping (46). Our experience is that laypersons may refer to this form of agonal breathing as “snoring.”

There is now abundant evidence in humans that that survival of patients with OHCA is as good as or better with bystander-initiated CCC CPR than with the previous guidelines in 2000 or earlier recommendations of 2:15 ventilations to chest compressions (Table 2). There is also evidence in a clinically realistic swine model of OHCA that neurologically intact survival is better with CCC CPR than with the newest 2005 guidelines-recommended 2:30 ventilations to chest compressions (39).

Our recommendations that “rescue breathing” or assisted ventilations are not necessary during cardiac arrest should not be construed to mean that we do not think oxygen delivery is important. On the contrary, adequate tissue oxygenation delivery is critically important, and early in cardiac arrest, CCC provides this crucial oxygen delivery (4).

Cerebral Perfusion During Chest Compressions for Cardiac Arrest

The importance of uninterrupted chest compressions in providing important cerebral perfusion was forcefully brought home to us as we listened to a recording of dispatch-directed CPR to a woman trying to resuscitate her husband. It must have taken some time for the paramedics to arrive because she returned later to the phone to ask the dispatcher, “Why is it that every time I press on his chest, he opens his eyes, and every time I stop to breathe for him, he goes back to sleep?” (47). What she was really asking was why is it every time I am doing chest compressions, he is not in coma, but every time I stop and perform so-called “rescue breathing,” he goes back into coma? During resuscitation efforts for cardiac arrest, brain perfusion is so marginal that any interruption in chest compressions, even for ventilations, has the potential of being deleterious. The recognition that perfusion, particularly cerebral perfusion, is more

important than ventilation early in cardiac arrest is why this new technique was labeled CCR.

Citizen Education in CCC CPR

A plausible reason that the guidelines have and continue to recommend both ventilations and chest compressions for all arrests is the concern that lay individuals cannot tell the difference between a primary cardiac arrest and a respiratory arrest, and therefore, patients with respiratory arrest will not receive needed ventilation if chest compression-alone CPR is advocated. Accordingly, it is important that the lay public be taught to call 911 if there are any questions and also to be able to distinguish between a respiratory and cardiac arrest.

If a layperson witnesses a sudden collapse of an adult, the usual approach of shake and shout should be performed. If there is no response, assess the breathing: is it normal or abnormal? Abnormal breathing means either no breathing at all or intermittent gasping. Snoring or gurgling respirations are types of gasping or agonal breathing. Such a victim should be treated as a cardiac arrest (46). If someone collapses after obviously choking at a restaurant, the appropriate response is to attempt to clear the airway with the Heimlich maneuver and then provide ventilation and chest compressions as needed. If someone is rescued from the water, assume that they need both chest compressions and ventilations, or “rescue breathing.” A person who has a drug or alcohol overdose, who is obtunded, and whose breathing slows and stops also needs assisted ventilations. The difference in these scenarios is not difficult to discern, even by a layperson, but must become a major focus of our public education.

New Protocols for EMS

Part of the rationale for the EMS portion of CCR is better understood in the context of the 3-phase time-sensitive model of cardiac arrest due to VF articulated by Weisfeldt and Becker (8). The first phase, the electrical phase, lasts about 4 to 5 min. During this phase, the most important intervention is defibrillation. This is why implanted cardioverter-defibrillators work and why the availability of AEDs and programs to encourage their use have saved lives in a wide variety of settings, including airplanes, airports, casinos, and some communities. The second phase to VF cardiac arrest is the circulatory phase, which lasts approximately from minute 4 or 5 to minute 15. During this time, the generation of adequate cerebral and coronary perfusion pressures by chest compressions before and after defibrillation is critical to neurologically normal survival. Ironically, if an AED is the first intervention applied during this phase, the subject is much less likely to survive (48). If pre-shock chest compressions are not provided, defibrillation during the circulatory phase almost always results in asystole or pulseless electrical activity (PEA). The previous recommendation for a stacked-shock protocol resulted in prolonged

interruption of essential chest compressions for rhythm analysis before and after shocks during this circulatory phase of cardiac arrest (49,50). Successful resuscitation of a patient with a pulseless rhythm usually requires pre-shock chest compressions and prompt effective resumption of chest compressions post-shock along with vasopressors. For these reasons, CCR recommends 200 chest compressions to provide myocardial perfusion prior to a single shock for VF in the circulatory phase and immediate application of another 200 chest compressions without prior assessment of the rhythm or pulse prior to the chest compressions (1,10).

In-hospital cardiac arrest may be different. Hopefully, most in-hospital VF cardiac arrests can be detected and treated during the electrical phase with immediate defibrillation. The National Registry of CPR of in-hospital cardiac arrests has shown that the majority are not VF but are rather non-VF arrests, many of which are noncardiac in etiology (51). In such cases, ventilation and chest compressions may be important.

Decreasing Chest Compression Interruptions

Another reason that survival of OHCA has been so poor is that paramedics, who almost always arrive after the electrical phase of VF cardiac arrest, spend only one-half of the time on the scene doing chest compressions (49,51). Interruptions in chest compressions were frequent when EMS personnel were following the previous guidelines. Emphasis on assessing and reassessing both the patient and the patient's electrical rhythm and the use of multiple stacked shocks for defibrillation contributed to significant chest compression interruptions. Although some of these recommendations might be appropriate in the electrical phase of VF arrest, when applied during the circulatory phase of VF cardiac arrest, these recommendations resulted in decreasing the number of chest compressions delivered and ultimately contributed to the poor outcomes over the last decade. The most recent guidelines were changed to a single VF shock in 2005 (52). This change for EMS resuscitation efforts has been part of CCR since 2003 (1,6,10).

Another major problem during resuscitation efforts by EMS personnel is endotracheal intubation. Endotracheal intubation has adverse effects due to the relatively long interruptions of chest compressions during placement and adverse effects of positive-pressure ventilation and frequent hyperventilation (13,53).

Accordingly, CCR discourages endotracheal intubation during the electrical and circulatory phases of cardiac arrest due to VF. Defibrillator pad electrodes are applied, and the patient is given 200 chest compressions and a single defibrillation shock that is immediately followed by 200 more chest compressions before the rhythm and pulse are analyzed (3).

Another of the more important aspects of CCR is that after the defibrillation shock, 200 additional chest compressions are provided before rhythm and pulse are analyzed.

This is based on our porcine model of OHCA. In the experimental laboratory, the animal is constantly monitored. We observed that after prolonged VF, a defibrillation shock rarely produced a perfusion rhythm. The VF will likely be terminated, but it almost always changes to either asystole or PEA. The key to successfully treating these post-defibrillation rhythms is urgent myocardial reperfusion. Chest compressions are of paramount importance after the defibrillation shock, especially in patients with PEA. In-dwelling, high-fidelity, micromanometer-tipped, solid-state, pressure-measuring catheters typically show small pulsatile increases in aortic pressure post-shock (a phenomenon called "pseudo-pulseless electrical activity"). Aortic pressures of 20/10 mm Hg are not uncommon in such a period. If hemodynamic support is provided by immediate chest compressions, these pressures often increase to 40/20 mm Hg and continue to increase until finally a perfusing and palpable pulse is realized. Without such immediate post-shock hemodynamic support provided by chest compressions, the aortic pressure will decline and soon be truly asystolic. Therefore, CCR calls for an additional 200 chest compressions immediately after the shock without a pause to assess the post-shock rhythm (1,3,10).

Excessive Positive-Pressure Ventilations Eliminated

Aufderheide et al. (14,53) have suggested that positive-pressure ventilation during VF arrest is detrimental. Based on both animal and clinical research, they have stated, "There is an inversely proportional relationship between mean intrathoracic pressure, coronary perfusion pressure, and survival from cardiac arrest" (54). Adverse effects of positive-pressure ventilation include an increase in intrathoracic pressure and the inability to develop a negative intrathoracic pressure during the release phase of chest compression (14,40,54). Positive-pressure ventilation inhibits venous return to the thorax and right heart and thus results in decreased coronary and cerebral pressures. Another aspect of hyperventilation and increased intrathoracic pressure is its adverse effect on intracranial pressure and cerebral perfusion pressure. These adverse effects are compounded by the fact that ventilation rates by physicians and paramedic rescuers are often excessive (mean of 37 compressions by both in-hospital resuscitation teams and out-of-hospital EMS services). Of note, retraining of EMS providers in this regard did not fully resolve their tendency to overventilate. Using their animal model to mimic their clinical out-of-hospital observation that excessive ventilation is common, these investigators found that hyperventilation not only increased the mean intrathoracic pressure, decreasing coronary perfusion pressure, but that 1-hour survival was less than in subjects not hyperventilated.

To avoid positive-pressure and excessive ventilations, CCR recommends opening the airway with an oropharyngeal device, placing a nonrebreather mask, and administrat-

ing high flow (about 10 l/min) oxygen (3). This is referred to as passive oxygen insufflation.

The CCR protocol is outlined in Figure 1.

First in Man Data

Kellum et al. (3) from Rock and Walworth counties in Wisconsin instituted CCR in 2004 (3). Using a historical control of the precedent 3 years following the 2000 AHA guidelines, they found a dramatic increase in neurologically intact survival with CCR. The mean survival to hospital discharge with intact neurologic function was 15% in the 3 years prior and 48% during the year when CCR was provided (3). These 1-year results in a small number of witnessed arrests were almost too good to believe, suggesting a significant “Hawthorne effect.” The Kellum et al. (5) 3-year experience with CCR has now been reported. Neurologic intact survival rate at hospital discharge was 40% (including 1 patient who received hypothermia) (5). Thus, there may well have been a slight Hawthorne effect during the first year. Nevertheless, in the subset of patients with witnessed cardiac arrest and shockable rhythm on arrival of the paramedics, there was dramatic improvement (15% to 40%) in neurologic intact survival at hospital discharge compared with the pre-CCR era (5) (Fig. 2).

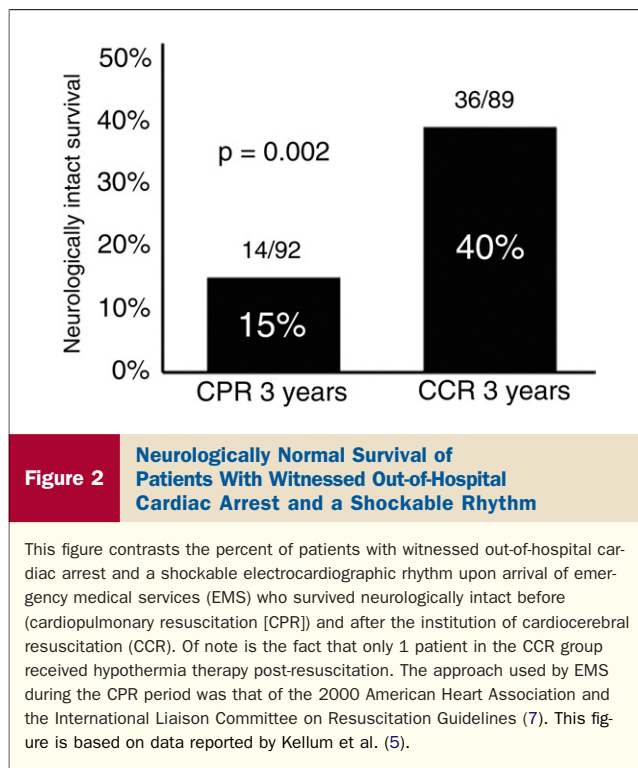
Bobrow et al. (4) instituted CCR (reported, as the editors required, as minimal-interruption cardiac resuscitation) in Arizona and found a >300% improvement (4.7% to 17.6%) in survival to hospital discharge in the subgroup of patients with witnessed cardiac arrest and shockable rhythm. These results are illustrated in Figure 3.

The Third Pillar of CCR Post-Resuscitation Care

Only about 25% of those initially resuscitated survive to leave the hospital. Among those initially resuscitated who do not survive long term, about one-third die from central nervous system damage, another one-third die from myocardial failure, and the final one-third from a variety of causes including infection and multiorgan failure (55).

Sunde et al. (56) in Norway formalized their post-resuscitation care and pursued an aggressive approach with such patients. Their approach emphasized providing therapeutic hypothermia to all who remained comatose post-resuscitation and performing early coronary angiography and percutaneous coronary intervention (PCI) in any patients with possible myocardial ischemia as a contributing factor to their cardiac arrests. Using this approach, they found a significant improvement in survival. During a control period from 1996 to 1998, 68 patients were admitted alive to the hospital after OHCA, but only 15 (26%) were alive 1 year later. During the period of their organized approach to formalize the treatment of post-resuscitation patients, the 1-year survival rate rose to 56% (56).

During this interventional period, 77% of all resuscitated victims had coronary angiography. The vast majority (96%) of those undergoing cardiac catheterization had documented



coronary disease, and 82% of those with documented coronary disease had total occlusions of an epicardial coronary vessel. These investigators performed coronary angiography for anyone post-resuscitation with ST-segment elevation on their admission ECG regardless of the consciousness state. They also took the same approach to those without ECG ST-segment elevation, but in those for which there was nonetheless a strong suspicion that myocardial ischemia was the underlying etiology of their cardiac arrests. A univariate analysis of their data revealed that reperfusion therapy was by far the most influential factor on survival, with an odds ratio of >27.

Finally, it is important to note that the neurologic status of long-term survivors during the experimental period of aggressive post-resuscitation care was excellent, with more than 90% having no neurologic deficits and 9% having mild deficits. These data suggest strongly that significant improvement in survival to discharge and even 1-year survival can be achieved with an aggressive and standardized approach to post-resuscitation care. Reperfusion therapy, either PCI or coronary artery bypass graft, had the most profound effect on outcome with an adjusted multivariate analysis odds ratio of 4.5. Of note, many of these patients were transported directly from the emergency department to the PCI suite upon arrival to the hospital (i.e., in an aggressive manner paralleling the current recommendation for certain ST-segment elevation myocardial infarction [STEMI] patients).

Importance of Therapeutic Hypothermia

The use of mild (32°C to 34°C) therapeutic hypothermia for comatose post-resuscitated cardiac arrest victims is accepted

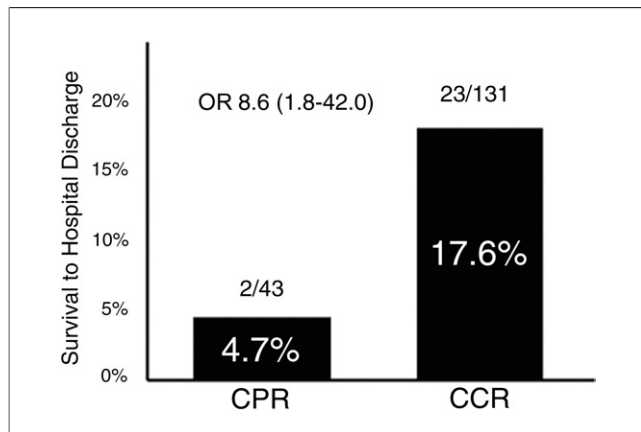


Figure 3 Survival to Hospital Discharge of Patients With Out-of-Hospital Cardiac Arrest Treated by 2 Different Emergency Medical Services Protocols

This figure contrasts the percent of patients with witnessed out-of-hospital cardiac arrest and shockable electrocardiographic rhythm on arrival of emergency medical services who survived to hospital discharge before and after the institution of a protocol similar to cardiocerebral resuscitation (CCR), except that it allowed ventilation by either passive oxygen insufflation or bag mask ventilation. This approach has been called minimally interrupted cardiac resuscitation. The approach used during the cardiopulmonary resuscitation (CPR) period was that of the 2000 American Heart Association and the International Liaison Committee on Resuscitation Guidelines (7). Of note is the fact that in this report, none of the patients received hypothermia therapy post-resuscitation. OR = odds ratio. This figure is based on data from Bobrow et al. (4).

by many resuscitation scientists. Two large, randomized, prospective trials published in 2002 showed improved survival and improved neurologic function of survivors when therapeutic hypothermia was used for comatose victims of OHCA (57,58). Great interest in how best to achieve rapid therapeutic hypothermia in this population has produced numerous additional reports (59-64). To assist communities and hospitals in beginning therapeutic hypothermia programs for resuscitated victims of cardiac arrest, a website and references with practical advice, including generalized orders to initiate hypothermia, are now available (65,66).

PCI Post-Resuscitation

The use of early cardiac catheterization and PCI in post-resuscitation patients has been further studied: Spaulding et al. (66) reported that neither clinical nor ECG findings in the post-resuscitation period, such as chest pain or ST elevation on the ECG, were good predictors of acute coronary occlusion. In other words, the ECG findings of acute coronary artery occlusion (ST-segment elevation) may not be apparent in the early post-resuscitation period. The question then arises: should nearly everyone who is successfully resuscitated from OHCA be taken to the catheterization laboratory for coronary angiography and potential emergency PCI? Several nonrandomized studies have examined this important question.

Quintero-Moran et al. (67) found in 2006 that among 13 patients with OHCA, they achieved a 54% survival to hospital discharge with aggressive early cardiac catheteriza-

tion and angioplasty strategy. Gorjup et al. (68) reported a series of 135 patients with STEMI and associated cardiac arrest. Survival to hospital discharge was achieved in 67%. Among the patients who were comatose (n = 86) at the time of cardiac catheterization, survival was achieved in 51%; the patients who were conscious after their cardiac arrests had a survival rate of 100% (68). Garot et al. (69) reported on 186 STEMI patients suffering cardiac arrest as a complication of their myocardial infarctions. Prior to cardiac catheterization, all of these patients were sedated and given neuromuscular blockage, hence their pre-catheterization neurologic status was not known. Fifty-five percent survived to hospital discharge, and among the survivors, 86% had normal neurologic function, 10% had mild disability, and 4% were severely neurologically disabled (69).

The combination of these 2 important resuscitation therapies, hypothermia and early PCI, was reviewed by Knafelj et al. (70). Their series contained 72 patients, all of whom were comatose post-resuscitation after cardiac arrest with signs of STEMI (70). Forty of the 72 patients received mild hypothermia and PCI, whereas 32 of the 72 underwent PCI only. The overall survival rate to hospital discharge was 61%, but there was a significant difference between those who were cooled pre-PCI and those who were not. Of those who received both angioplasty and hypothermia, the hospital discharge survival rate was 75%, with 73% of those survivors having good neurologic function. Among those who did not receive hypothermia, 44% were discharged from the hospital and only 16% had normal neurologic function (70).

Combining these studies gives an approximate survival rate to hospital discharge of 62% for those who have cardiac arrest and require resuscitation with STEMI, with 79% of

Table 3 Comparison Between Cardiocerebral Resuscitation and AHA CPR

Cardiocerebral Resuscitation 2003	AHA 2005 Guidelines and 2008 Advisory Statement
Continuous CC for bystanders	Bystander "hands-only" CPR
Decrease rescue breathing	Decrease CC interruptions
BLS: No rescue breaths	BLS: 30:2 CCs to ventilations
ACLS: Passive oxygen insufflation or limited breaths/min	ACLS: 8-10 breaths/min
200 CCs prior to shock	Optional 5 cycles of 30:2 prior to shock
Single shock	Single shock
200 CCs immediately after shock	5 cycles of 30:2 immediately after shock
Therapeutic hypothermia for all unconscious post-resuscitation	Therapeutic hypothermia for all unconscious post-resuscitation from VFCA
Early, emergent catheterization and PCI for all resuscitated victims regardless of electrocardiographic findings	No official statement

ACLS = advanced cardiac life support; AHA = American Heart Association; BLS = basic life support; CC = chest compression; CPR = cardiopulmonary resuscitation; PCI = percutaneous coronary intervention; VFCA = ventricular fibrillation cardiac arrest.

all survivors having intact neurologic function. This is much better than what has historically been achieved without moderate hypothermia, early cardiac catheterization, and PCI when indicated.

It is our opinion that for optimal results with CCR, aggressive post-resuscitation care that includes both the use of therapeutic hypothermia and emergent cardiac catheterization and PCI when appropriate must be included. Thus, this third component has been recently added to our protocol of CCR.

Conclusions

Cardiocerebral resuscitation was begun in November 2003 in Tucson, Arizona, and by 2007 was being used throughout the majority of the state. In 2005, the AHA updated their guidelines and incorporated some of the changes made with CCR (52). In 2008, the AHA published a science advisory statement supporting chest compressions only for bystander response to adult cardiac arrest (71). Table 3 compares current aspects of CCR with the AHA 2005 guidelines and their 2008 advisory statement.

Uninterrupted perfusion to the heart and brain by CCC prior to defibrillation during cardiac arrest is essential to neurologically normal survival. The low incidence of bystander-initiated resuscitation efforts in patients with cardiac arrest is a major public health problem. We have long advocated CCC CPR by bystanders as a solution to this critical issue because eliminating mouth-to-mouth “rescue breathing” will go a long way toward increasing the incidence of bystander-initiated resuscitation efforts. It is exciting to see that a technique (chest compression-only CPR) that had not been heretofore formally taught results in the same or better neurologically normal survival rates than those achieved with techniques taught for decades. CCR also changes the approach of those delivering ACLS. These changes resulted in dramatic (250% to 300%) improvement in survival of patients most likely to survive: those with witnessed cardiac arrest and shockable rhythm. More aggressive post-resuscitation care, including hypothermia and emergent cardiac catheterization and PCI, is required to save even more victims of sudden cardiac arrest.

Reprint requests and correspondence: Dr. Gordon A. Ewy, University of Arizona Sarver Heart Center, University of Arizona College of Medicine, Tucson, Arizona 85724. E-mail: gaewy@aol.com.

REFERENCES

- Ewy G. Cardiocerebral resuscitation: the new cardiopulmonary resuscitation. *Circulation* 2005;111:2134–42.
- Kern KB, Valenzuela TD, Clark LL, et al. An alternative approach to advancing resuscitation science. *Resuscitation* 2005;64:261–8.
- Kellum MJ, Kennedy KW, Ewy GA. Cardiocerebral resuscitation improves survival of patients with out-of-hospital cardiac arrest. *Am J Med* 2006;119:335–40.
- Bobrow BJ, Clark LL, Ewy GA, et al. Minimally interrupted cardiac resuscitation by emergency medical services providers for out-of-hospital cardiac arrest. *JAMA* 2008;299:1158–65.
- Kellum MJ, Kennedy KW, Barney R, et al. Cardiocerebral resuscitation improves neurologically intact survival of patients with out-of-hospital cardiac arrest. *Ann Emerg Med* 2008;52:244–52.
- Ewy G. A new approach for out-of-hospital CPR: a bold step forward. *Resuscitation* 2003;58:271–2.
- American Heart Association, in collaboration with the International Liaison Committee on Resuscitation. Guidelines for cardiopulmonary resuscitation and emergency cardiac care: international consensus on science. *Circulation* 2000;102:I22–59.
- Weisfeldt M, Becker L. Resuscitation after cardiac arrest: a 3-phase time-sensitive model. *JAMA* 2002;288:3035–8.
- Ewy GA. Cardiocerebral resuscitation: the new cardiopulmonary resuscitation. *Circulation* 2005;111:2134–42.
- Kern K, Valenzuela T, Clark L, et al. An alternative approach to advancing resuscitation science. *Resuscitation* 2005;64:261–8.
- Berg MD, Clark LL, Valenzuela TD, Kern KB, Berg RA. Post-shock chest compression delays with automated external defibrillator use. *Resuscitation* 2005;64:287–91.
- Berg RA, Hilwig RW, Kern KB, Ewy GA. Precountershock cardiopulmonary resuscitation improves ventricular fibrillation median frequency and myocardial readiness for successful defibrillation from prolonged ventricular fibrillation: a randomized, controlled swine study. *Ann Emerg Med* 2002;40:563–70.
- Milander MM, Hiscok PS, Sanders AB, Kern KB, Berg RA, Ewy GA. Chest compression and ventilation rates during cardiopulmonary resuscitation: the effects of audible tone guidance. *Acad Emerg Med* 1995;2:708–13.
- Aufferdeide TP, Lurie KG. Death by hyperventilation: a common and life-threatening problem during cardiopulmonary resuscitation. *Crit Care Med* 2004;32:S345–51.
- 2005 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care: part 2: adult basic life support. *Circulation* 2005;112 Suppl I:III5–16.
- Zheng ZJ, Croft JB, Giles WH, Mensah GA. Sudden cardiac arrest in the United States. *Circulation* 2001;104:2158–63.
- Zipes DP, Camm AJ, Borggrefe M, et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death—executive summary: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death). *J Am Coll Cardiol* 2006;48:1064–108.
- Centers for Disease Control and Prevention. State-specific mortality from sudden cardiac death—United States, 1999. *MMWR Morb Mortal Wkly Rep* 2002;51:123–6.
- Standards for cardiopulmonary resuscitation (CPR) and emergency cardiac care (ECC). II: basic life support. *JAMA* 1974;227:833–68.
- Standards and guidelines for cardiopulmonary resuscitation (CPR) and emergency cardiac care (ECC). *JAMA* 1980;244:453–509.
- Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Guidelines for cardiopulmonary resuscitation and emergency cardiac care. *JAMA* 1992;268:2171–302.
- Eckstein M, Stratton S, Chan L. Cardiac arrest resuscitation evaluation in Los Angeles: CARE-LA. *Ann Emerg Med* 2005;45:504–9.
- Van Hoeyweghen RJ, Bossaert LL, Mullie A, et al. Quality and efficiency of bystander CPR: Belgian Cerebral Resuscitation Study Group. *Resuscitation* 1993;26:47–52.
- Hallstrom A, Cobb L, Johnson E, Copass M. Cardiopulmonary resuscitation by chest compression alone or with mouth-to-mouth ventilation. *N Engl J Med* 2000;342:1546–53.
- Waalewijn RA, Tijssen JG, Koster RW. Bystander initiated actions in out-of-hospital cardiopulmonary resuscitation: results from the Amsterdam Resuscitation Study (ARRESUST). *Resuscitation* 2001;50:273–9.
- Cardiopulmonary resuscitation by bystanders with chest compression only (SOS-KANTO): an observational study. *Lancet* 2007;369:920–6.
- Iwami T, Kawamura T, Hiraide A, et al. Effectiveness of bystander-initiated cardiac-only resuscitation for patients with out-of-hospital cardiac arrest. *Circulation* 2007;116:2900–7.

28. Bohm K, Rosenqvist M, Herlitz J, Hollenberg J, Svensson L. Survival is similar after standard treatment and chest compression only in out-of-hospital bystander cardiopulmonary resuscitation. *Circulation* 2007;116:2908–12.
29. Rea TD, Helbock M, Perry S, et al. Increasing use of cardiopulmonary resuscitation during out-of-hospital ventricular fibrillation arrest: survival implications of guideline changes. *Circulation* 2006;114:2760–5.
30. Steen S, Liao Q, Pierre L, Paskevicius A, Sjöberg T. The critical importance of minimal delay between chest compressions and subsequent defibrillation: a haemodynamic explanation. *Resuscitation* 2003;58:249–58.
31. Becker L, Berg R, Pepe P, et al. A reappraisal of mouth-to-mouth ventilation during bystander-initiated cardiopulmonary resuscitation. A statement for healthcare professionals from the Ventilation Working Group of the Basic Life Support and Pediatric Life Support Subcommittees, American Heart Association. *Circulation* 1997;96:2102–12.
32. Standards and guidelines for cardiopulmonary resuscitation (CPR) and emergency cardiac care (ECC). *JAMA* 1986;255:2905–89.
33. SOS-KANTO Study Group. Cardiopulmonary resuscitation by bystanders with chest compression only (SOS-KANTO): an observational study. *Lancet* 2007;369:920–6.
34. Ewy GA. Cardiac arrest—guideline changes urgently needed. *Lancet* 2007;369:882–4.
35. Abella BS, Aufderheide TP, Eigel B, et al. Reducing barriers for implementation of bystander-initiated cardiopulmonary resuscitation. A scientific statement from the American Heart Association for healthcare providers, policymakers, and community leaders regarding the effectiveness of cardiopulmonary resuscitation. *Circulation* 2008;117:704–9.
36. Ewy GA. Cardiopulmonary resuscitation—strengthening the links in the chain of survival. *N Engl J Med* 2000;342:1599–601.
37. Assar D, Chamberlain D, Colquhoun M, et al. Randomized controlled trials of staged teaching for basic life support. 1. Skill acquisition at bronze stage. *Resuscitation* 2000;45:7–15.
38. Kern KB, Hilwig RW, Berg RA, Sanders AB, Ewy GA. Importance of continuous chest compressions during cardiopulmonary resuscitation: improved outcome during a simulated single lay-rescuer scenario. *Circulation* 2002;105:645–9.
39. Ewy GA, Zuercher M, Hilwig RW, et al. Improved neurological outcome with continuous chest compressions compared with 30:2 compressions-to-ventilations cardiopulmonary resuscitation in a realistic swine model of out-of-hospital cardiac arrest. *Circulation* 2007;116:2525–30.
40. Aufderheide TP, Sigurdsson G, Pirralo RG, et al. Hyperventilation-induced hypotension during cardiopulmonary resuscitation. *Circulation* 2004;109:1960–5.
41. Becker LB, Berg RA, Pepe PE, et al. A reappraisal of mouth-to-mouth ventilation during bystander-initiated cardiopulmonary resuscitation: a statement for healthcare professionals from the Ventilation Working Group of the Basic Life Support and Pediatric Life Support Subcommittees, American Heart Association. *Ann Emerg Med* 1997;30:654–66.
42. Ruben H. The immediate treatment of respiratory failure. *Br J Anaesth* 1964;36:542–9.
43. Lawes EG, Baskett PJF. Pulmonary aspiration during unsuccessful cardiopulmonary resuscitation. *Intensive Care Med* 1987;13:379–82.
44. Virkkunen I, Kujala S, Ryyänen S, et al. Bystander mouth-to-mouth ventilation during bystander-initiated cardiopulmonary resuscitation. *J Intern Med* 2006;260:39–42.
45. Meursing BT, Wulterkens DW, van Kesteren RG. The ABC of resuscitation and the Dutch (re) treat. *Resuscitation* 2005;64:279–86.
46. Ewy GA. Cardiology patient page. New concepts of cardiopulmonary resuscitation for the lay public: continuous-chest-compression CPR. *Circulation* 2007;116:e566–8.
47. Berg RA, Kern KB, Sanders AB, Otto CW, Hilwig RW, Ewy GA. Bystander cardiopulmonary resuscitation. Is ventilation necessary? *Circulation* 1993;88:1907–15.
48. Cobb L, Fahrenbruch C, Walsh T, Compass M, Olsufka M. Influence of cardiopulmonary resuscitation prior to defibrillation in patients with out-of-hospital ventricular fibrillation. *JAMA* 1999;281:1182–8.
49. Valenzuela T, Kern K, Clark L, et al. Interruptions of chest compressions during emergency medical systems resuscitations. *Circulation* 2005;112:1259–65.
50. Wik L, Hansen TB, Fylling F, et al. Delaying defibrillation to give basic cardiopulmonary resuscitation to patients with out-of-hospital ventricular fibrillation: a randomized trial. *JAMA* 2003;289:1389–95.
51. Wik L, Kramer-Johansen J, Myklebust H, et al. Quality of cardiopulmonary resuscitation during out-of-hospital cardiac arrest. *JAMA* 2005;293:299–304.
52. International Liaison Committee on Resuscitation. 2005 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. *Resuscitation* 2005;67:181–341.
53. Aufderheide T, Sigurdsson G, Pirralo R, et al. Hyperventilation-induced hypotension during cardiopulmonary resuscitation. *Circulation* 2004;109:1960–5.
54. Aufderheide TP. The problem with and benefit of ventilations: should our approach be the same in cardiac and respiratory arrest? *Curr Opin Crit Care* 2006;12:207–12.
55. Schoenenberger RA, von Planta M, von Planta I. Survival after failed out-of-hospital resuscitation. Are further therapeutic efforts in the emergency department futile? *Arch Intern Med* 1994;154:2433–7.
56. Sunde K, Pytte M, Jacobsen D, et al. Implementation of a standardised treatment protocol for post resuscitation care after out-of-hospital cardiac arrest. *Resuscitation* 2007;73:29–39.
57. Hypothermia after Cardiac Arrest Study Group. Mild hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med* 2002;346:549–56.
58. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med* 2002;346:557–63.
59. Kim F, Olsufka M, Carlom D, et al. Pilot study of rapid infusion of 2 L of 40°C normal saline for induction of mild hypothermia in hospitalized, comatose survivors of out-of-hospital cardiac arrest. *Circulation* 2005;112:715–9.
60. Kim F, Olsufka M, Longstreth WT Jr., et al. Pilot randomized clinical trial of prehospital induction of mild hypothermia in out-of-hospital cardiac arrest patients with a rapid infusion of 4°C normal saline. *Circulation* 2007;115:3064–70.
61. Tiainen M, Poutiainen E, Kovala T, Takkunen O, Hoppola O, Roine RO. Cognitive and neurophysiological outcome of cardiac arrest survivors treated with therapeutic hypothermia. *Stroke* 2007;38:2303–8.
62. Arrich J. Clinical application of mild therapeutic hypothermia after cardiac arrest. *Crit Care Med* 2007;35:1041–7.
63. Belliard G, Catez E, Charron C, et al. Efficacy of therapeutic hypothermia after out-of-hospital cardiac arrest due to ventricular fibrillation. *Resuscitation* 2007;75:252–9.
64. Kamarainen A, Virkkunen J, Tenhunen J, Yli-Hankala A, Silfvast T. Prehospital induction of therapeutic hypothermia during CPR: a pilot study. *Resuscitation* 2008;76:360–3.
65. University of Chicago: Emergency Resuscitation Center. Available at: <http://hypothermia.uchicago.edu/>. Accessed October 24, 2008.
66. Spaulding SM, Joly L-M, Rosenberg A, et al. Immediate coronary angiography in survivors of out-of-hospital cardiac arrest. *N Engl J Med* 1997;336:1629–33.
67. Quintero-Moran B, Moreno R, Villarreal S, et al. Percutaneous coronary intervention for cardiac arrest secondary to ST-elevation acute myocardial infarction. Influence of immediate paramedical/medical assistance on clinical outcome. *J Invasive Cardiol* 2006;18:269–72.
68. Gorjup V, Radsel P, Kocjancic ST, Erzen D, Noc M. Acute ST-elevation myocardial infarction after successful cardiopulmonary resuscitation. *Resuscitation* 2007;72:379–85.
69. Garot P, Lefevre T, Eltchaninoff H, et al. Six-month outcome of emergency percutaneous coronary intervention in resuscitated patients after cardiac arrest complicating ST-elevation myocardial infarction. *Circulation* 2007;115:1354–62.
70. Knafelj R, Radsel P, Ploj T, Noc M. Primary percutaneous coronary intervention and mild induced hypothermia in comatose survivors of ventricular fibrillation with ST-elevation acute myocardial infarction. *Resuscitation* 2007;74:227–34.
71. Sayre MR, Berg RA, Cave DM, Page RL, White RD. Hands-only (compression-only) cardiopulmonary resuscitation—a call to action for bystander response to adults who experience out-of-hospital sudden cardiac arrest. *Circulation* 2008;117:2162–7.

Key Words: CPR ■ cardiocerebral ■ resuscitation ■ ventricular fibrillation.

Recent Advances in Cardiopulmonary Resuscitation: Cardiocerebral Resuscitation

Gordon A. Ewy, and Karl B. Kern
J. Am. Coll. Cardiol. 2009;53;149-157
doi:10.1016/j.jacc.2008.05.066

This information is current as of March 10, 2010

Updated Information & Services	including high-resolution figures, can be found at: http://content.onlinejacc.org/cgi/content/full/53/2/149
Supplementary Material	Supplementary material can be found at: http://content.onlinejacc.org/cgi/content/full/53/2/149/DC1
References	This article cites 70 articles, 35 of which you can access for free at: http://content.onlinejacc.org/cgi/content/full/53/2/149#BIBL
Citations	This article has been cited by 3 HighWire-hosted articles: http://content.onlinejacc.org/cgi/content/full/53/2/149#otherarticles
Rights & Permissions	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://content.onlinejacc.org/misc/permissions.dtl
Reprints	Information about ordering reprints can be found online: http://content.onlinejacc.org/misc/reprints.dtl